CHAPTER 31

# Menopause

Debra A. Ahern

The World Health Organization, as well as the Stages of Reproductive Aging Workshop (STRAW), define menopause as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation. Natural menopause is recognized only after 12 months of amenorrhea that is not associated with either a pathologic (e.g., Sheehan syndrome) or physiologic cause (e.g., lactation). Most women achieve natural menopause between the ages of 47 and 55. Perimenopause, a time of hormonal fluctuations, with or without menstrual irregularities, may precede the final menses by 2 to 8 years.

Menopause is a gradual, physiologic process that occurs as part of natural aging and frequently does not require medical intervention. Many women make the transition from regular menses to menopause with little difficulty and few symptoms. For others symptoms such as hot flashes, vaginal dryness, and dyspareunia significantly affect their quality of life. As life expectancy increases, women may spend greater than one third of their life in the postmenopausal years. Issues associated with aging and health maintenance, such as osteoporosis prevention and cardiovascular risk reduction, are addressed elsewhere.

## Symptoms

- Hot flashes—Sudden intense sensation of heat, usually starting with the scalp, face, neck, or chest and lasting 2 to 10 minutes +++
- Nocturnal hyperhydrosis—Awakening to damp clothing, sheets, hair +++
- Diaphoresis ++
- Chills

## Workup

- History: personal
  - Age at menarche
  - Length of cycle
  - Duration and quantity of flow
  - First day of last menses
  - Menstrual irregularities
  - Obstetric history
  - Surgical history
  - Thromboembolic disorders
  - Cardiovascular disease, HTN, diabetes, dyslipidemia

- Mood disorders—Depression or anxiety, postpartum depression, premenstrual syndrome
- Cancer
- Medications—Prescription, nonprescription, and herbal

- History: family
  - Age of menopause of first-degree relatives
  - Cancer—Breast, uterus, ovarian
  - Osteoporosis
  - Cardiovascular disease
- History: social
  - Tobacco, alcohol, recreational drugs
  - Marital status
  - Children—Empty nest
  - Aging parents
  - Employment or financial
- Physical examination
  - Pelvic and breast examination
  - Vital signs, including height and weight
  - Examination of other systems as directed by history

### Comments and Treatment Considerations

Laboratory tests are seldom helpful due to cyclic hormonal fluctuations as well as variations from person to person. Neither the American Academy of Family Practice, the American College of Physicians, or the American College of Obstetricians and Gynecologist (ACOG) make recommendations regarding the diagnosis of menopause. The North American Menopause Society states that FSH and estradiol levels are of limited value in confirming perimenopause but *consistently* elevated FSH levels greater than 30 are indicative of menopause. The American Association of Clinical Endocrinologists recommends measurements of FSH and states that levels greater than 40 are diagnostic of menopause but caution that during perimenopause, levels may be intermittently elevated.

Consider urinary chorionic gonadotropin (UCG), FSH, LH, prolactin, CBC, TSH, and PPD as directed by your history and examination. Inhibin levels and vaginal ultrasounds to measure ovarian volumes and number of antral follicles lack the sensitivity and specificity of less invasive and less costly measures. Other studies may include Papanicolaou (Pap), mammography, DEXA, coagulation studies, lipid profile, glucose, and urodynamic assessments, as indicated by history and examination.

Lifestyle modifications are necessary. Avoid triggers including warm air and hot, spicy food and beverages. Dress in layers and remove to cool off as necessary. Focus on paced respirations (slow deep, diaphragmatic breathing at a rate of 6 to 10 respirations per minute). Exercise-active women report fewer hot flashes; make a daily exercise regimen part of your routine. Quit smoking; smokers experience more hot flashes than nonsmokers.

When lifestyle modifications are not enough, consider supplementing with the following:

- Estrogen (with progesterone as needed): start with low dose
  - 0.3 mg conjugated equine estrogen
  - 0.5 mg micronized estradiol
  - 25 μg transdermal estradiol
  - 2.5 μg ethynyl estradiol
  - Low-dose birth control pills (nonsmokers only)
  - 50 to 100 μg estradiol vaginal ring (Femring)
- Progesterone alone (not FDA approved for this indication)
  - 400 mg medroxyprogesterone acetate (Depo-Provera)
  - 20 to 80 mg/day micronized megestrol acetate (Megace)
- Other
  - 37.5 to 150 mg venlafaxine (Effexor) (FDA approved)
  - Fluoxetine (Prozac) (FDA approved)
  - 12.5 to 25 mg paroxetine (Paxil)
  - 300 to 900 mg gabapentin (Neurontin)
  - 0.1 to 0.3 mg/day transdermal patch clonidine
- Herbal—Supported by randomized controlled studies
  - Black cohosh (8 mg/day). Caution with breast cancer patients—ACOG states that black cohosh may be helpful in the short term.
- Conflicting studies
  - Soy—Patients should be advised to consider the caloric intake of soy supplements
- Not supported by randomized controlled studies
  - Dong quai
  - Evening primrose oil
  - Red clover
  - Ginseng
  - Wild yam
  - Ginkgo biloba
  - Valerian root
  - Flaxseed

The exact etiology of hot flashes is unknown. Although estrogen has been shown to be the most effective treatment for hot flashes, research has failed to demonstrate a difference in estrogen levels between those who suffer from hot flashes and those who do not. Left untreated, the majority of hot flashes stop spontaneously within 5 to 6 years, but in up to 10% of women they may last well into the eighth decade. In women with an intact uterus, estrogen should always be given with progestin to prevent endometrial hyperplasia. Changing the route of estrogen from oral to transdermal may help ameliorate intractable hot flashes by bypassing the liver. Estrogen should always be prescribed for the shortest time possible at the lowest effective dose and serious consideration should be given to stopping it within 5 years. Data from the Women's Health Initiative did show an increase in the rate of breast cancer when both estrogen and progesterone were used (38 versus 30 per 10,000 person-years) but not with unopposed estrogen. The Nurses' Health Study found a 30% higher rate of breast cancer in women taking estrogen alone for 10 years. Low-dose estrogen regimens (e.g., 0.3 mg of conjugated equine estrogen) have not been adequately studied. Other risks of hormonal therapy include an increase in strokes, venous

thromboembolism, coronary events, and worsening of lipid profiles. For nonsmokers requiring birth control, low dose OCPs may be considered. Periodically, patients may be withdrawn from the pills and an FSH level drawn 1 to 2 weeks later. A low level indicates that a patient is not yet menopausal, but a high level does not confirm menopause. Patients should be advised to use alternative forms of birth control until 12 months after the last menses.

Contraindications to hormone replacement therapy include vaginal bleeding of unknown etiology, active liver disease, coronary heart disease, history of endometrial cancer, history of thromboembolic disease, and history of breast cancer (controversial). Relative contraindications include migraine headaches, triglycerides in excess of 400, active gallbladder disease, fibroids, atypical ductal hyperplasia of the breast, and more than one first-degree relative with breast cancer.

## MENSTRUAL IRREGULARITIES/ POSTMENOPAUSAL BLEEDING

The hallmark of the perimenopausal years is the unpredictability of the intermenstrual cycle length and the variability of the volume and pattern of flow. Few studies are available that have addressed this issue. Bleeding that occurs in women not on hormone replacement therapy after 1 year past the final menses requires evaluation. Although most postmenopausal bleeding is due to benign processes (e.g., vaginal or endometrial atrophy, submucosal fibroids, polyps or endometrial hyperplasia), endometrial carcinoma is found approximately 10% of the time.

### Symptoms
- Missed menses
- Frequent menses
- Changes in length of flow and/or quantity of flow
- Menorrhagia
- Postmenopausal bleeding ++

### Signs
- Pallor
- Irregular uterine contour
- Enlarged or atrophied uterus
- Atrophic vaginal mucosa

### Workup
- History
  - LMP
  - Length and quantity of flow
  - Precipitating factors—Trauma, postcoital
  - Associated symptoms—Pain, fever, vaginal discharge, urinary symptoms, rectal bleeding, vasomotor symptoms

- Age at menarche
- Obstetric history
- Cycle length and regularity
- Presence of vasomotor symptoms
- Medications—Prescribed (OCPs, HRT, warfarin, psychotropics), OTC (ASA, NSAIDs), herbal
- Coagulopathies
- Smoking, alcohol, recreational drugs
- Medical history with emphasis on hepatic, renal, and thyroid disorders

- Physical examination
  - Vital signs
    - Pelvic examination—Assess size, contour, and tenderness of uterus, and note any suspicious lesions, lacerations, or foreign bodies. Assess the mucosa for atrophy and determine the origin of bleeding (rectal, urethral, genital).
    - Cardiovascular
    - Skin examination with emphasis on ecchymosis and petechia
    - Examination of nailbeds, conjunctiva for pallor
- Lab tests
  - Pap should be done in all women with unexplained bleeding with colposcopy and biopsy of any suspicious lesions
  - CBC with differential
  - Reticulocyte count
  - Iron studies
  - Coagulation studies
  - TSH
- Transvaginal ultrasound—Often the initial test in women with unexplained postmenopausal bleeding, an endometrial stripe of more than 5 mm has a 96% sensitivity and 61% specificity for the detection of cancer. Endometrial biopsy (Do indications need to be checked? Is there any postmenopausal bleeding?) is required if the stripe exceeds 5 mm or there is diffuse or increased echogenicity or inadequate visualization of the endometrium. For women on HRT, the sensitivity is similar, but there is a higher false-positive rate due to an average greater endometrial thickness.
- Endometrial biopsy—Less invasive and costly than a dilation and curettage (D&C), endometrial biopsy has about the same sensitivity and specificity. However, only about 5% to 15% of the endometrial surface is sampled and up to 70% of the samples are nondiagnostic
- Hysteroscopy—More costly and invasive than other evaluations, provides direct visualization of the endometrium and allows for targeted biopsy or excision of lesions
- Saline infusion sonography—May detect small lesions missed by transvaginal ultrasound, but provides no tissue for pathology
- MRI may be helpful in further evaluating lesions found initially on sonography (e.g., fibroids, adenomyosis)

### Comments and Treatment Considerations

Treatment of vaginal bleeding, whether perimenopausal or postmenopausal, is dependent on the underlying diagnosis. Perimenopausal

woman who require contraception and who do not smoke may be placed on low-dose OCPs. The Mirena intrauterine device (IUD) has also been proven to substantially decrease bleeding. Smokers should be encouraged to stop but may be cycled on progesterone.

Evaluation of postmenopausal bleeding in women on HRT depends on the regimen. Women on cyclic therapy may continue to bleed. No evaluation is needed for women on continuous regimens whose bleeding begins and resolves within 6 to 9 months of initiation of therapy.

## PSYCHOSOCIAL ISSUES

Natural menopause occurs at a time of life when many other changes are occurring. Many symptoms commonly associated with menopause are not due to the decline in ovarian function but to the aging process and the social changes accompanying midlife.

### Signs

- Insomnia increases in both genders. +++
- Decline in memory, difficulty in thinking or other cognitive disturbances +++

### Comments and Treatment Considerations

The relationship of changing hormones and mood disorders (28% to 41%) is unclear. A history of depression, anxiety, premenstrual disorder, life stresses, and general health are the major predictors of psychiatric problems during midlife. Evidence that hormone replacement improves mood is weak. No correlation has been found between menopausal status and the prevalence of arthralgias, joint stiffness, fatigue, and other somatic complaints.

## SEXUAL DYSFUNCTION

Although studies have shown that approximately 40% of women stop sexual activity between the ages of 40 and 60, the association of sexual dysfunction and declining hormone levels has not been clearly established. Evidence is strong that vaginal dryness increases in many women as the menopausal transition proceeds.

### Symptoms

- Decreased libido +++
- Vaginal dryness +++
- Dyspareunia ++

### Signs

- Thin friable atrophic vaginal mucosa
- Caruncle
- Vaginal stenosis

### Workup

- History
  - Pain or burning with urination

- Frequent urinary tract infections
- Painful intercourse
- Feeling of vaginal dryness

- Laboratory
  - Seldom helpful—Consider biopsy as needed

### Comments and Treatment Considerations

With low-dose vaginal estrogen therapy, systemic absorption is minimal. Progesterone should be considered for women with an intact uterus but is usually not necessary. Small studies involving only 20 women found endometrial hyperplasia in only 1 after 6 months of 0.3-mg Premarin cream therapy. None of 10 women using Estring with vaginal bleeding demonstrated hyperplasia on endometrial biopsy.

The use of testosterone for sexual dysfunction is controversial and not FDA approved. Women who have undergone surgical menopause are most likely to benefit from androgens. Potential side effects include hirsutism, acne, and decreasing high-density lipoprotein (HDL) levels.

Sexual intercourse improves vaginal blood flow, thus maintaining an acidic vaginal pH, promoting normal vaginal flora and a healthy mucosal epithelium. Vaginal weights strengthen pelvic floor musculature and may improve awareness of sexual arousal in women with orgasmic disorders.

Nonpharmacologic lifestyle changes can include frequent intercourse and increased tactile stimulation, smoking cessation, strength training and aerobic exercise, vaginal moisturizers (e.g., Replens), vaginal lubricants (water-soluble preferable, e.g., Astroglide), vaginal weights, and a clitoral suction device (Eros-Clitoral Therapy Device, UroMetrics, Inc., St. Paul, MN ).

Pharmacologic therapies can include systemic estrogen therapy (see vasomotor instability); low-dose vaginal conjugated estrogen (0.3 mg of conjugated estrogen daily intravaginally for 3 weeks, twice weekly thereafter); 0.5 g crystalline estradiol (Estrace); 25 μg estradiol tablet intravaginally twice weekly; estradiol vaginal ring (Estring), which releases 6 to 9 mcg estradiol daily for 3 months; testosterone 1.22 to 2.5 mg/day methyltestosterone; combinations estrogen/methyltestosterone 5 mg twice daily of micronized oral testosterone.

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